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Carnitine-Acylcarnitine Translocase Deficiency

Synonym: CACT Deficiency

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Summary

Clinical characteristics

Carnitine-acylcarnitine translocase (CACT) is a critical component of the carnitine shuttle, which facilitates the transfer of long-chain fatty acylcarnitines across the inner mitochondrial membrane. CACT deficiency causes a defect in mitochondrial long-chain fatty acid β-oxidation, with variable clinical severity. Severe neonatal-onset disease is most common, with symptoms evident within two days after birth; attenuated cases may present in the first months of life. Hyperammonemia and cardiac arrhythmia are prominent in early-onset disease, with high rates of cardiac arrest. Other clinical features are typical for disorders of long-chain fatty acid oxidation: poor feeding, lethargy, hypoketotic hypoglycemia, hypotonia, transaminitis, liver dysfunction with hepatomegaly, and rhabdomyolysis. Univentricular or biventricular hypertrophic cardiomyopathy, ranging from mild to severe, may respond to appropriate dietary and medical therapies. Hyperammonemia is difficult to treat and is an important determinant of long-term neurocognitive outcome. Affected individuals with early-onset disease typically experience brain injury at presentation, and have recurrent hyperammonemia leading to developmental delay / intellectual disability. Affected individuals with later-onset disease have milder symptoms and are less likely to experience recurrent hyperammonemia, allowing a better developmental outcome. Prompt treatment of the presenting episode to prevent hypoglycemic, hypoxic, or hyperammonemic brain injury may allow normal growth and development.

Diagnosis/testing

Characteristic elevation of long-chain acylcarnitines C16, C18, and C18:1 on acylcarnitine profile suggests a diagnosis of CACT or CPT II deficiency. The diagnosis of CACT deficiency is confirmed by identification of biallelic pathogenic variants in *SLC25A20*, or in some cases by identifying reduced CACT enzyme activity in skin fibroblasts.

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Management

Routine daily treatment of manifestations: The mainstay of therapy is a high-carbohydrate diet (>60% of total caloric intake) with restriction of long-chain dietary fat (to <10% of total calories) and treatment with the anaplerotic agent triheptanoin (to provide 25%-35% of total calories). If triheptanoin is not available, medium-chain triglyceride (MCT) oil (10%-30% of total calories) could be used as a substitute. Fasting is avoided or limited, and carnitine supplemented at ~100 mg/kg/day is recommended. Goals of care include optimization of caloric intake to avoid or reduce hyperammonemia (ammonia scavenger medications are of limited efficacy in this condition) and aggressive rehabilitation therapy, including physical and occupational therapy, to address motor delays. Placement of a feeding tube and/or feeding therapy may be required in those with feeding issues.

Emergency treatment of manifestations: Administration of high-dextrose-containing fluids: oral/enteral carbohydrate polymer (at home) or intravenous dextrose (in the hospital). Hyperammonemia is most sensitive to high rates of dextrose infusion (12-15 g/kg/day glucose for infants and 10-12 g/kg/day for children age 1-6 years), while ammonia scavenging medications (sodium benzoate, sodium phenylbutyrate) are of limited efficacy. Cardiac arrhythmias, cardiomyopathy, rhabdomyolysis, and acute renal impairment should be treated per standard of care, typically in the intensive care unit. Consideration should be given for triheptanoin treatment in those with cardiogenic shock.

Prevention of secondary complications: A home emergency plan for prompt illness management should be provided to parents, primary care providers, teachers, and school staff. When undergoing surgeries or procedures (e.g., dental interventions or neuroimaging requiring sedation), pre-procedure hospital management includes IV dextrose with electrolytes appropriate for age. Provide the family with an emergency plan and letter for use during emergency department visits.

Surveillance: Regular evaluations by a metabolic specialist and metabolic dietitian. Measurement of growth parameters (including head circumference) and monitoring of developmental milestones at each visit. Neuropsychological testing using age-appropriate tools as clinically indicated. Laboratory monitoring to include serum ammonia level, total CK level, ALT, AST, glucose, electrolytes, and albumin levels for periodic surveillance as clinically indicated. Measurement of complete blood count, ferritin level, prealbumin, CRP, essential fatty acids, calcium, magnesium, phosphate, copper, zinc, selenium, folate, and vitamins A, D, E, and B_{12} annually after the first year of life. Measurement of plasma electrolytes, creatinine, blood urea nitrogen, and/or cystatin C levels for renal monitoring as clinically indicated. Echocardiogram to assess for cardiomyopathy or cardiac dysfunction annually and as clinically indicated. EKG or 24-hour Holter test periodically, as clinically indicated. Consider EEG or neuroimaging in those with new neurologic symptoms or altered mental status.

Agents/circumstances to avoid: Prolonged fasting, catabolic illness (fever, intercurrent infection), inadequate caloric provision during times of catabolic stress (including during fasting), prolonged strenuous physical activity, and prolonged administration of anesthetics containing high levels of long-chain fatty acids (e.g., propofol).

Evaluation of relatives at risk: Testing of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment of CACT deficiency. For at-risk newborn sibs when prenatal testing was not performed, in parallel with newborn screening either test for the familial *SLC25A20* pathogenic variants or measure acylcarnitine profile.

Genetic counseling

CACT deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SLC25A20* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial

SLC25A20 pathogenic variants and being unaffected. Heterozygotes (carriers) are asymptomatic. Once the *SLC25A20* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

Carnitine acylcarnitine translocase (CACT) is a part of the carnitine shuttle that is localized to the inner mitochondrial membrane. It transfers long-chain acylcarnitines formed by the action of carnitine palmitoyl-transferase I (CPT1) in the outer mitochondrial membrane into the mitochondrial matrix in exchange for free carnitine. These acylcarnitines are then converted into acyl-CoA by carnitine palmitoyl-transferase 2 (CPT2) to enter β-oxidation [Indiveri et al 2011].

No consensus clinical diagnostic criteria for carnitine-acylcarnitine translocase (CACT) deficiency have been published.

Suggestive Findings

Scenario 1: Abnormal newborn screening (NBS) result. NBS for CACT deficiency is primarily based on quantification of the acylcarnitine analytes on dried blood spots by tandem mass spectrometry. See also ACMG ACT Sheet.

C16 and C18:1 acylcarnitine values above the cutoff reported by the screening laboratory are considered positive and require follow-up biochemical testing, as these metabolites could also be elevated in carnitine palmitoyltransferase II (CPT2) deficiency (see Differential Diagnosis). Some screening laboratories have used the C16+C18:1/C2 ratio as a marker for both conditions. Cutoff values vary among screening laboratories.

Most individuals with the severe early-onset phenotype will already be symptomatic by the time a newborn screening result is available. After a positive newborn screening test, the newborn should be evaluated immediately and a follow-up plasma acylcarnitine profile obtained [Yan et al 2017, Tang et al 2019, Habib et al 2021].

If the follow-up biochemical testing supports the likelihood of CACT deficiency, additional testing is required to establish the diagnosis (see Establishing the Diagnosis).

Medical interventions should be put in place immediately on receipt of an abnormal NBS result, while additional testing is performed to establish a definitive diagnosis of CACT deficiency.

- Arrange for an immediate clinical evaluation to include:
  - Clinical assessment for poor feeding, lethargy, hypotonia, cardiac insufficiency, respiratory distress, and hepatomegaly;
  - Measurement of screening serum glucose, ammonia, creatine kinase (CK), and transaminase levels.
- If a newborn is symptomatic or has abnormal screening laboratory results, the following medical interventions should be initiated (see also Management):
  - Admit to the hospital for further evaluation.
  - Initiate a diet based on a high carbohydrate intake and long-chain fatty acid restriction.
  - Start triheptanoin or medium-chain triglyceride (MCT) oil (if triheptanoin is not available).
  - Start carnitine supplementation.
- If a newborn is asymptomatic and has normal screening laboratory results:
  - Provide counseling to the family regarding feeding, at-home monitoring of clinical status, and emergency procedures and contact information.
  - While awaiting diagnostic confirmation (see Establishing the Diagnosis) consider initiating the dietary interventions for symptomatic newborns as well as triheptanoin (or MCT oil).

Note: Decisions regarding medical interventions in this scenario are influenced by the specific initial screening results as well as turnaround time for confirmatory testing at the medical center involved.

Scenario 2: Symptomatic individual who has either atypical findings associated with untreated neonatal-onset CACT deficiency or later-onset CACT deficiency resulting from any of the following:

- NBS results returned after the onset of symptoms
- NBS not performed
- False negative NBS result
- Caregivers not adherent to recommended treatment following a positive NBS result

Supportive (but nonspecific) clinical, imaging, and preliminary laboratory findings can include the following.

Clinical findings

- Poor feeding
- Tachypnea
- Cardiac arrhythmia and/or cardiac arrest
- Seizures
- Neurologic impairment, including encephalopathy, lethargy, and/or hypotonia
- Muscle weakness
- Hepatomegaly

Imaging findings. Cardiomyopathy with hypertrophy and depressed ejection fraction on echocardiogram

Laboratory findings

- Hypoketotic hypoglycemia
- Hyperammonemia ranging from 85 to >1000 µmol/L
- Elevated blood lactate
- Metabolic acidosis
- Elevated liver enzymes (AST, ALT) ± evidence of synthetic dysfunction (low albumin, elevated prothrombin, and elevated INR)
- Elevated creatine kinase levels ranging from 190 to >25,000 U/L
- Acylcarnitine profile demonstrating low free carnitine, elevated C16-, C16:1-, C18-, and C18:1-acylcarnitines (This profile is indistinguishable from CPT II deficiency, and thus follow-up testing is required to establish the diagnosis; see Establishing the Diagnosis.)
- Urine organic acid analysis demonstrating dicarboxylic aciduria with or without lactic aciduria

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of CACT deficiency **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *SLC25A20* by molecular genetic testing (Table 1) or – in limited instances – by significantly reduced activity of the enzyme carnitine-acylcarnitine translocase in cultured skin fibroblasts [Rubio-Gozalbo et al 2004]. Because of its relatively high sensitivity, *SLC25A20* molecular genetic testing can obviate the need for enzymatic testing, and thus is the preferred confirmatory test for CACT deficiency [Costa et al 2003].

Note: (1) Per ACMG variant interpretation criteria, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to pathogenic variants in this section is understood

to include any likely pathogenic variants. (2) identification of biallelic *SLC25A20* variants of uncertain significance (or identification of one known *SLC25A20* pathogenic variant and one *SLC25A20* variant of uncertain significance) does not establish or rule out the diagnosis; in this case enzymatic testing may be required.

When NBS results and other laboratory findings suggest the diagnosis of CACT deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SLC25A20* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A fatty acid oxidation disorders multigene panel** that includes *SLC25A20* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Carnitine-Acylcarnitine Translocase (CACT) Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SLC25A20	Sequence analysis [3]	90%-93% [4]
	Gene-targeted deletion/duplication analysis [5]	7%-10% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes on 3p21.31 (e.g., those described Stenson et al [2020]) may not be detected by these methods.

Enzymatic analysis in skin fibroblasts. Enzyme levels <1% (compared to control) are suggestive of the severe neonatal form while levels between 1% and 10% are suggestive of the later-onset form [Olpin et al 1997, Iacobazzi et al 2004a].

Clinical Characteristics

Clinical Description

Individuals with carnitine-acylcarnitine translocase (CACT) deficiency can experience variable clinical severity. To date, just over 100 individuals have been reported with CACT deficiency. Two phenotypes have been described: a severe neonatal-onset form and a later-onset form.

Severe Neonatal Form

The clinical features of severe CACT deficiency generally present around age two days, prior to receipt of the newborn screening result. Clinical features include poor feeding, hypotonia, lethargy, arrhythmias, hypoketotic hypoglycemia, hyperammonemia, transaminitis, liver dysfunction with hepatomegaly, and rhabdomyolysis [Rubio-Gozalbo et al 2004, Vitoria et al 2015, Ryder et al 2021]. Most individuals who have been reported did poorly [Vitoria et al 2015, Ryder et al 2021]. However, there have been a limited number of surviving individuals (> 1 year of age) with development ranging from normal to moderate developmental delay and/or intellectual disability, the latter two (developmental delay and intellectual disability) being the most common outcomes [Lee et al 2007, Pierre et al 2007, Vatanavicharn et al 2015, Vitoria et al 2015, Chinen et al 2020, Ryder et al 2021].

Cardiac arrhythmias. The most prominent cardiac feature in the neonatal period is arrhythmia, particularly ventricular tachycardia, followed by various tachyarrhythmias and bradyarrhythmias [Korman et al 2006, Chong et al 2017, Tang et al 2019, Ryder et al 2021]. The following have also been reported [Hsu et al 2001, Ryder et al 2021]:

- First-degree atrioventricular block
- Left bundle branch block
- Right bundle branch block
- Broad complex tachyarrhythmia
- Atrial flutter

Cardiomyopathy. Most affected individuals develop univentricular or biventricular hypertrophic cardiomyopathy, ranging from mild to severe and varying in age of onset from a few days to several years/childhood [Pande et al 1993, Iacobazzi et al 2004a, Al-Sannaa & Cheriyan 2010, Vatanavicharn et al 2015, Tang et al 2019, Chinen et al 2020, Ryder et al 2021]. Cardiac dysfunction due to reduced left ventricular ejection fraction (<55%) is common. Cardiac findings generally improve as metabolic stabilization is reached through dietary management, carnitine supplementation, or anaplerotic therapy in some cases (see Management) [Iacobazzi et al 2004b, Chinen et al 2020, Ryder et al 2021].

Metabolic derangements can include hypoketotic hypoglycemia, hyperammonemia, transaminitis, liver dysfunction, lactic acidosis, metabolic acidosis, and rhabdomyolysis, all of which can improve with immediate or long-term interventions (see Management). Long-term survivors may continue to experience chronic hyperammonemia and mild-to-moderate hyperCKemia [Ryder et al 2021]; the latter may in some cases be induced or exacerbated by increased physical activity [Authors, personal observation].

Gastrointestinal issues. In individuals who survive long term, feeding issues may persist and use of a feeding tube, including gastrostomy, is often necessary:

- Hepatomegaly may be present at the time of diagnosis or may develop months later [Vitoria et al 2015, Gürbüz et al 2021].
- Steatohepatitis, hepatomegaly, gallstones, and liver fibrosis have been reported as potential longer-term complications [Ryder et al 2021].
- Chronic diarrhea has also been reported.

- One individual had upper gastrointestinal bleeding, possibly secondary to chronic liver disease [Vatanavicharn et al 2015].

Neurologic findings. In addition to hypotonia, affected individuals may also develop tonic-clonic seizures [Vitoria et al 2015, Chinen et al 2020]. This may be due to hypoglycemic/hypoxic brain injury and dietary interventions do not necessarily lead to improvement or resolution of the seizure disorder.

Developmental delay / intellectual disability. Most affected individuals have mild-to-moderate developmental delay and/or intellectual disability. A small number of affected individuals who were diagnosed early and have undergone appropriate treatment have resulting normal growth and development [Lee et al 2007, Pierre et al 2007, Vatanavicharn et al 2015, Vitoria et al 2015, Chinen et al 2020, Ryder et al 2021]. Contributing factors for neurodevelopmental delay are brain injury at presentation (often due to cardiac arrest) and the subsequent frequency and severity of metabolic decompensations featuring hyperammonemia. However, because of the relatively small number of diagnosed individuals, further studies assessing neurocognitive skills are required to provide a better understanding of developmental outcomes.

Neuroimaging. In a small number of affected individuals, neuroimaging has demonstrated cerebral edema, intracranial bleeding, acute ischemia involving the middle cerebral arteries, or moderate cortical loss with delayed myelination [Iacobazzi et al 2004a, Al-Sannaa & Cheriyan 2010, Chinen et al 2020, Ryder et al 2021].

Renal abnormalities may include nephromegaly, renal Fanconi syndrome, proximal renal tubular acidosis, and acute renal injury [Pande et al 1993, Vitoria et al 2015, Ryder et al 2021]. The pathophysiology and natural history of these findings in relation to dietary therapies are unclear.

Prognosis. The severe, neonatal-onset form is often associated with marked enzyme deficiency (<1% of activity) and, if not diagnosed or treated in a timely fashion, death in infancy (<12 months). A limited number of individuals have reached early or late childhood and a couple have survived into early adulthood. From these, only one adult individual appears to remain asymptomatic [Ryder et al 2021].

- In those who survive longer term, there continues to be a risk for acute metabolic decompensation, particularly in the presence of metabolic stressors such as acute illnesses or fasting periods (e.g., due to surgical procedures) [Vitoria et al 2015].
- Chronic or recurrent hyperammonemia is a major factor in neurologic outcome.
- Other chronic health issues include elevated CK levels (hyperCKemia), cardiac arrhythmias, and cardiomyopathy [Iacobazzi et al 2004b, Chinen et al 2020, Ryder et al 2021].

Causes of death. The most common cause of death is cardiac arrest secondary to arrhythmias (ventricular tachycardia) [Ryder et al 2021]. Other causes include sudden cardiac death, septicemia, or shock secondary to acute infections [Nuoffer et al 2000, Korman et al 2006, Vitoria et al 2015, Tang et al 2019, Ryder et al 2021]. A small number of affected individuals have died because of Reye syndrome or upper GI bleeding in early childhood [Fukushima et al 2013, Vatanavicharn et al 2015]. Postmortem studies have shown steatosis of multiple tissues including myocardium, liver, proximal renal tubules, vascular endothelium, and skeletal myocytes [Morris et al 1998, Yang et al 2001, Korman et al 2006, Vatanavicharn et al 2015, Chinen et al 2020].

Later-Onset Form

A small group of affected individuals experience symptoms after age one month; a fraction of these manifest symptoms after age one year [Olpin et al 1997, Wang et al 2011, Vitoria et al 2015, Ryder et al 2021]. Due to a suggestive family history, a few individuals have been diagnosed either in utero or shortly after birth and have remained asymptomatic under adequate therapy [Yang et al 2001, Iacobazzi et al 2004a, Ryder et al 2021].

Table 2. Select Features of Later-Onset Carnitine-Acylcarnitine Translocase (CACT) Deficiency at Time of Diagnosis

Feature	% of Persons w/Feature	Comment
Hypoketotic hypoglycemia	70%	Some have developed this finding during/after an acute infection, while in others no trigger for metabolic decompensation has been identified.
Cardiac problems	40%	Incl reduced ejection fraction, left ventricular hypertrophy, hypertrophic cardiomyopathy, ventricular tachycardia, asystole &/or cardiac arrest
Respiratory problems	30%	Tachypnea, hypoxemia, apnea, & respiratory failure
Hyperammonemia	20%	Can exceed 100 µmol/L
Elevated transaminases	20%	
HyperCKemia	20%	Can exceed 200 U/L
Metabolic acidosis &/or lactic acidosis	20%	

Clinical features in individuals who have the later-onset form are similar to those seen in the neonatal-onset form, but with symptoms (hypoketotic hypoglycemia, hyperammonemia, muscle weakness, hypotonia, lethargy) that are typically milder. For some affected individuals, the first manifestation of CACT deficiency was heart failure and ventricular tachycardia [Lee et al 2011]. Others have presented with failure to thrive and jaundice [Lee et al 2011, Vitoria et al 2015].

Prognosis. Enzyme activity is typically between 1% and 10% of controls [Olpin et al 1997, Iacobazzi et al 2004a]. However, enzyme activity should not entirely guide the prognosis, as there are individuals with enzyme activity in the 1%-10% range who had clinical features consistent with the severe neonatal form [Morris et al 1998, Iacobazzi et al 2004a, Vitoria et al 2015, Ryder et al 2021].

- There is less risk of chronic hyperammonemia and, although rare, long-term survival into adulthood with normal neurocognitive progress has been described [Ryder et al 2021].
- Only one known individual with the later-onset form has remained asymptomatic into adulthood [Ryder et al 2021].

Genotype-Phenotype Correlations

Neonatal-Onset Form

c.199-10T>G (formerly c.261-10T>G or -10T>G intron 2). Homozygosity for this pathogenic splice site variant is associated with the severe neonatal-onset form [Vatanavicharn et al 2015].

- Affected individuals who have one pathogenic c.199-10T>G allele and another pathogenic variant on the other allele tend to have severe clinical features, with no apparent correlation to survival [Hsu et al 2001, Tang et al 2019].
- The c.199-10T>G pathogenic variant is the most common pathogenic variant described to date, and the most common pathogenic variant observed in individuals of East Asian and Southeast Asian descent, suggesting a possible founder effect [Ogawa et al 2000, Lee et al 2011, Wang et al 2011].

c.270delC (p.Phe91fs). Homozygosity for this pathogenic deletion of Turkish origin has been correlated with the severe neonatal-onset form of CACT deficiency [Hsu et al 2001, Gürbüz et al 2021].

c.713A>G (p.Gln238Arg). Homozygosity for this pathogenic variant of Middle Eastern origin has also been correlated with the severe neonatal-onset form of CACT deficiency [Al Aqeel et al 2003, Galron et al 2004, Iacobazzi et al 2004b].

Milder Neonatal-Onset or Later-Onset Form

c.82G>T (p.Gly28Cys). Homozygosity for this missense pathogenic variant is correlated with either a milder early-onset or a later-onset form of CACT deficiency [Morris et al 1998, Ryder et al 2021]. Most individuals with this pathogenic variant have been of Pakistani or Indian descent [Morris et al 1998, Ryder et al 2021].

Nomenclature

In the past, CACT deficiency was also referred to as:

- CATR deficiency, a different acronym that also stands for carnitine-acylcarnitine translocase deficiency [Brivet et al 1996];
- Carnitine-acylcarnitine carrier (CAC) deficiency [Huizing et al 1997].

Prevalence

To date, 89 individuals with the neonatal-onset form of CACT deficiency and 14 individuals with the later-onset form have been described.

Based on newborn screening data, the estimated incidence of CACT in an aggregate population of individuals from Australia, Germany, and the United States is approximately 1:750,000-1:2,000,000 [Lindner et al 2010], while the estimated incidence in Hong Kong and Taiwan is 1:60,000 and 1:400,000, respectively [Chien et al 2013, Hui et al 2014]. The higher incidence in East Asian populations could be a reflection of the prevalence of the pathogenic c.199-10T>G variant (see Genotype-Phenotype Correlations and Table 10).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC25A20*.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Carnitine-Acylcarnitine Translocase Deficiency

Gene	Disorder	MOI	Laboratory Findings	Comment
ACADVL	Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	AR	Hypoketotic hypoglycemia, hyperammonemia, hyperCKemia (myopathic form), transaminitis, altered hepatic synthetic function (hepatic form); ↑ C14, C14:1, C14:2 & C12 in acylcarnitine profile	Early-onset cardiac & multiorgan failure in VLCAD deficiency can be reminiscent of CACT deficiency, but acylcarnitine profile is quite different.
CPT2	Carnitine palmitoyltransferase II (CPT II) deficiency	AR	Hypoketotic hypoglycemia, hyperammonemia, hyperCKemia; ↑ C16 & C18:1 in serum/plasma acylcarnitines.	CPT2 & CACT deficiency have similar acylcarnitine profiles & are indistinguishable at presentation at birth & through NBS. Molecular genetic testing &/or enzyme activity is required.
TANGO2	*TANGO2*-related metabolic encephalopathy and arrhythmias	AR	Hypoglycemia, lactic acidosis, mild hyperammonemia, hyperCKemia., transaminitis; ↑ C10 or C14:1 in acylcarnitine profile (during acute episode) & marked ketoacidosis w/lactic acidosis in urine organic acids	*TANGO2*-related metabolic encephalopathy is assoc w/↑ risk for motor & intellectual disability, brain abnormalities, hypothyroidism, seizures, & adrenal insufficiency. Onset age is variable.

AR = autosomal recessive; CACT = carnitine-acylcarnitine translocase; MOI = mode of inheritance; NBS = newborn screening

Management

No consensus clinical practice guidelines for carnitine-acylcarnitine translocase (CACT) deficiency have been published.

When CACT deficiency is suspected during the diagnostic evaluation (i.e., due to elevated C16 and C18:1 on acylcarnitine profile), metabolic treatment should be initiated immediately.

Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure, obesity) require a multidisciplinary approach including multiple subspecialists, with oversight and expertise from a specialized metabolic center.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with CACT deficiency, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis of Carnitine-Acylcarnitine Translocase (CACT) Deficiency

Evaluation	Comment
Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian [1]	• Transfer to specialist center w/experience in mgmt of inherited metabolic diseases (strongly recommended) • Consider short hospitalization at a center of expertise for inherited metabolic conditions to provide caregivers w/detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for acute encephalopathic crises).
Baseline metabolic evals	Serum glucose, serum ammonia, total CK level, serum carnitine levels, plasma acylcarnitine profile
Baseline cardiologic evals	• EKG to assess for arrhythmia • Echocardiogram to assess for cardiomyopathy & cardiac dysfunction • Consider referral to cardiologist. [2]
Liver dysfunction	• Plasma AST, ALT, hepatic synthetic function tests (albumin, prothrombin, INR, platelet count) • Abdominal ultrasound to assess for hepatomegaly & nephromegaly (rare) • Referral to hepatologist as clinically indicated
Baseline renal assessment	• Serum BUN, creatinine &/or cystatin C, electrolytes • Abdominal ultrasound to assess for nephromegaly (rare) & hepatomegaly • Referral to nephrologist as clinically indicated
Consultation w/neurologist	Consider referral if evidence of seizures or epilepsy.
Consultation w/psychologist &/or social worker	To ensure understanding of diagnosis & assess parents' & affected person's coping skills & resources
Developmental assessment	Consider referral to a developmental pediatrician if concerns for developmental delay or intellectual disability.
Consultation w/PT, OT, & speech therapist	Consider referral if evidence of developmental delays.
Genetic counseling by genetics professionals [3]	To inform affected persons & families re nature, MOI, & implications of CACT deficiency in order to facilitate medical & personal decision making

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; MOI = mode of inheritance; OT = occupational therapist; PT = physical therapist

1. After a new diagnosis of CACT deficiency in a child, the closest hospital and local pediatrician should also be informed.

2. Implantation of a pacemaker may be considered (see Table 7).

3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

All children with CACT deficiency require the supervision of a specialist metabolic dietitian with experience in managing diet in individuals with long-chain fatty acid oxidation disorders (LC-FAODs). Management may differ between centers, but dietetic management of CACT deficiency typically follows the general principles of management of severe LC-FAODs.

Table 5. Routine Daily Treatment in Individuals with Carnitine-Acylcarnitine Translocase (CACT) Deficiency

Principle/Manifestation	Treatment	Considerations/Other
Restriction of dietary long-chain fat to prevent accumulation of toxic long-chain acylcarnitines	A high-carbohydrate diet is recommended (typically >60% of total calories) w/restriction of long-chain dietary fat (<10% of total calories) & normal-high caloric intake. [1]	• Oils such as walnut or flaxseed are prescribed to meet essential fatty acid requirements. [2] • Skimmed breast milk has been used to limit its long-chain fatty acid content to 6%-7% of total calories. [3]
Avoidance of fasting (See also Agents / Circumstances to Avoid.)	• Provide frequent meals & limit overnight fasting to inhibit lipolysis. • Duration of fasting interval depends on severity of illness & age of affected person	• Continuous overnight feeds may be recommended in infancy & early childhood to restrict overnight fasting. • Late-night uncooked cornstarch may be used instead of continuous overnight feeds in older or less severely affected persons
Anaplerotic therapy	Triheptanoin (Dojolvi®) (10%-35% of total calories)	• Synthetic medium-chain fatty acid w/7 carbons; provides 2 acetyl-CoA molecules, a 3-carbon propionyl-CoA, & 4 5-carbon ketone bodies [4] • The provision of both even- & odd-chain ketone bodies → superior TCA cycle anaplerosis. [4] • However, evidence for triheptanoin use in CACT deficiency is limited. • Its safety & efficacy have been described in 5 patients, 3 of whom presented w/cardiogenic shock. [5] • Excluded from the initial open-label multicenter safety & efficacy study, persons w/CACT deficiency were then included in the extension study, suggesting a reduction of major clinical events (MCE) rate. [6] • Triheptanoin may contribute to osmotic diarrhea.
Supplementation w/medium-chain triglyceride (instead of triheptanoin)	Medium-chain triglyceride (MCT) supplementation (10%-30% of total calories) as C8 oil or MCT formula (e.g., Monogen®, LIPIstart™)	• Allows energy generation & ketogenesis through β-oxidation of medium-chain fatty acids [7] • Fatty acyl moieties of C10 length or longer (which are dependent on the carnitine shuttle) account for 20%-50% of total fatty acids in most commercially available MCT formulas. Partial utilization of these may be the reason ketogenesis on MCT formula is suboptimal in CACT deficiency. Some centers thus prefer a fat-free formula supplemented w/C8 oil. • MCT may contribute to osmotic diarrhea.

Table 5. continued from previous page.

Principle/Manifestation	Treatment	Considerations/Other
Detoxification of long-chain acyl-CoA intermediates	Carnitine supplementation, 50-200 mg/kg/d divided BID or TID [8]	• Carnitine supplementation in LC-FAO has been controversial due to previous mouse models showing signs of cardiotoxicity following L-carnitine administration. [9] • However, cumulative experience in persons w/CACT suggests that supplementation does not → cardiotoxicity. [8] • Additionally, carnitine can facilitate export of excess (& sometimes toxic) long-chain fatty acyl CoA as acylcarnitines & improve levels of free carnitine. [8] • May contribute to osmotic diarrhea
Chronic hyperammonemia	Optimization of caloric intake (see first row above) is the foremost intervention to avoid or ↓ hyperammonemia.	• Ammonia scavengers (sodium benzoate, sodium phenylbutyrate) are of limited efficacy in this condition. • Carbaglu (carglumic acid), a structural analog to NAG & allosteric activator of carbamoyl phosphate synthetase 1 (CPS1), has been used off-label in 2 affected persons, 1 of whom had a successful & stable outcome. [10] • CACT deficiency has been proposed to ↓ acetyl-CoA & therefore NAG (essential in the urea cycle). [11] • High dietary carbohydrate intake appears necessary to prevent chronic recurrent hyperammonemia but may → excessive weight gain & steatohepatitis. [12]
Addressing ↑ energy/ caloric demands	Nasogastric tube, fundoplication, gastrostomy, or jejunostomy to address feeding issues	• Feeding difficulties are common in early childhood. • Gastrostomy placement allows provision of enteral emergency regimen to ensure adequate caloric intake during illness.
Gross motor delay	• Physical therapy • Occupational/feeding therapy • Aggressive rehab therapy	Adequate provision of information & education to parents, affected persons, & caregivers

NAG = N-acetylglutamate; TCA = tricarboxylic acid
1. Rohr [2015]
2. Mahapatra et al [2018], Ryder et al [2021]
3. Kritzer et al [2020]
4. Roe & Brunengraber [2015], Mahapatra et al [2018], Guffon et al [2021]
5. Roe & Brunengraber [2015], Vockley et al [2016], Mahapatra et al [2018]
6. Vockley et al [2017], Vockley et al [2022]
7. Gillingham et al [2006]
8. Rubio-Gozalbo et al [2004], Roe & Brunengraber [2015], Ryder et al [2021]
9. Liebig et al [2006], Primassin et al [2008], Spiekerkoetter et al [2009], Knottnerus et al [2018]
10. Vitoria et al [2015], LiverTox [2016], Author [personal observation]
11. Röschinger et al [2000]
12. Ryder et al [2021]

Table 6. Emergency Outpatient Treatment in Individuals with Carnitine-Acylcarnitine Translocase (CACT) Deficiency

Manifestation	Treatment	Considerations/Other
Mildly ↑ catabolism [1]	• Carbohydrate supplementation orally or via tube feed [2] • ↑ carnitine supplementation [3]	• Trial of outpatient treatment at home for up to 12 hrs could be considered based on degree of symptoms. • Reassessment (every ~2 hrs) for clinical changes [4]

Table 6. continued from previous page.

Manifestation	Treatment	Considerations/Other
Fever	Administration of antipyretics (acetaminophen, ibuprofen) if fever >38.5°C	Immediate clinical eval recommended to determine status
Occasional vomiting	Antiemetics [5]	

1. Fever <38.5°C (101°F); enteral or gastrostomy tube feeding tolerated without recurrent vomiting or diarrhea; absence of neurologic symptoms (altered consciousness, irritability, hypotonia, dystonia)
2. Stringent guidelines to quantify carbohydrate/caloric requirements are available to guide nutritional arrangements in the outpatient setting, with some centers recommending provision of carbohydrate-rich beverages every two hours, with frequent reassessment.
3. Temporarily increasing L-carnitine doses (e.g., to 200 mg/kg/day in infants) may be considered [Rubio-Gozalbo et al 2004, Roe & Brunengraber 2015, Ryder et al 2021].
4. Alterations in mentation/alertness, fever, and enteral feeding tolerance; discuss any new or evolving clinical features with the designated center of expertise for inherited metabolic diseases.
5. Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food and beverages at home or during transfer to hospital.

Acute manifestations (e.g., lethargy, encephalopathy, seizures, or progressive coma), often occurring in the setting of intercurrent illness and/or inadequate caloric intake, should be managed symptomatically and with generous caloric support in a hospital setting, with aggressive treatment and supportive care of any identified or clinically suspected metabolic stressors (see Table 7).

Table 7. Acute Inpatient Treatment in Individuals with Carnitine-Acylcarnitine Translocase (CACT) Deficiency

Manifestation	Treatment [1]	Considerations/Other
↑ catabolism (due to fever, perioperative/peri-interventional fasting periods,repeated vomiting/diarrhea)	• Administer high-energy (dextrose-containing) fluids & (if needed) insulin for mgmt of hyperglycemia. [2, 3] • IV L-carnitine supplementation [4, 5] • Address electrolytes & pH imbalances w/IV fluid mgmt.	• Obtain blood glucose, electrolytes, BUN, creatinine, AST/ALT, albumin, blood gases, serum ammonia, total CK level, & plasma acylcarnitine profile. • Cardiac monitoring is indicated. • Ongoing assessment of hemodynamic status & for new neurologic signs is critical. • Use of carnitine supplementation is controversial (see Table 5, **Considerations/Other**). While there is no evidence of cardiotoxicity directly triggered by IV administration, the authors recommend slow IV administration to ↓ any potential risk. [5] • Inadequate or delayed start of emergency treatment → high risk of consequent long-term neurodisability.
Signs of fatigue, abnormal heart rate or rhythm, hypotension or signs of cardiac failure	• Place a cardiac monitor. • Obtain an EKG. • Consider echocardiogram if not previously obtained or if signs of cardiac deterioration from baseline. • Consult a cardiologist; placement of a pacemaker may be considered.	Triheptanoin has been used successfully as rescue therapy in the presence of severe cardiac complications (cardiogenic shock). [6]

Table 7. continued from previous page.

Manifestation	Treatment [1]	Considerations/Other
Clinical myalgia, muscle tenderness, &/or urinary discoloration	• Assess for rhabdomyolysis. • Improve caloric & fluid intake. • Administer IV fluids; consider initial saline bolus based on CK levels. • Avoid nephrotoxic medications or agents during this event. • Consult a nephrologist.	Request labs listed in 1st row (serum ammonia, glucose, electrolytes, etc.) w/emphasis on plasma CK & urinalysis for assessment of rhabdomyolysis.
New or evolving neurologic symptoms (i.e., muscular hypotonia, irritability, rigors, dystonia, ↓ consciousness)	• Initiate treatment above for ↑ catabolism. • Obtain serum ammonia levels. • Consult neurologist if evidence of seizure or signs of encephalopathy to consider EEG or neuroimaging.	If hyperammonemia is present, see following row.
Hyperammonemia	Optimize & maximize caloric intake through high-energy (dextrose containing) fluids. See 1st row for details.	• Monitor free-flowing serum ammonia every 2-4 hrs or as clinically indicated. • Protein restriction is often unsuccessful; ↑ caloric intake through carbohydrates is most effective. • Although apparently w/o success, a few authors have used nitrogen scavengers (sodium benzoate, sodium phenylacetate or sodium phenylbutyrate) or intravenous arginine during initial presentation in the setting of persistently ↑ ammonia w/altered mental status (despite caloric optimization). [7] • Extracorporeal ammonia clearance could be considered if medical therapy fails.

BUN = blood urea nitrogen; CK = creatine kinase; IV = intravenous

1. Inpatient emergency treatment should: (1) take place at the closest medical facility, (2) be started without delay, and (3) be supervised by physicians and specialist dietitians at the responsible metabolic center, who should be contacted without delay. While there may be different presenting symptoms (e.g., myalgia, fatigue), a complete evaluation including cardiac assessment and comprehensive laboratory tests should always be requested, as the patient's clinical status could progress in severity.

2. Intravenous glucose solutions should provide 12-15 g/kg/day glucose for infants and 10-12 g/kg/day for children 12 months - 6 years.

3. Use of insulin if hyperglycemia emerges; IV insulin given at a starting dose of 0.025 IU/kg/hour in the event of persistent hyperglycemia (>150-180 mg/dL in plasma, or glucosuria).

4. L-carnitine (with options to increase the dose) can be given intravenously, which enhances bioavailability.

5. Evans & Fornasini [2003], Nasser et al [2012]

6. Vockley et al [2016], Mahapatra et al [2018], Vockley et al [2022]

7. Al Aqeel et al [2003], Vitoria et al [2015], Yan et al [2017], Tang et al [2019], Kritzer et al [2020], Habib et al [2021]

Transitional care from pediatric to adult-centered multidisciplinary care settings. CACT deficiency is a lifelong disorder with varying implications depending on clinical presentation; smooth transition of care from the pediatric setting is essential for long-term management, which should be multidisciplinary, integrating resources of all relevant subspecialties. Standardized procedures for transitional care do not exist for CACT deficiency due to the absence of multidisciplinary outpatient departments.

- Transitional care concepts have been developed in which adult internal medicine specialists initially see individuals with CACT deficiency together with pediatric metabolic experts, dietitians, psychologists, and social workers.

- As the long-term course of pediatric metabolic diseases in this age group is not yet fully characterized, continuous supervision by a center of expertise with metabolic diseases with sufficient resources is essential.

Prevention of Primary Manifestations

High carbohydrate intake (typically >60%), long-chain dietary fat restriction (<10%), and triheptanoin (Dojolvi®) or MCT oil (instead of triheptanoin) supplementation remain the cornerstone of CACT deficiency treatment. Although management of any given affected individual is nuanced and managed on a case-by-case basis, minor illnesses, where caloric needs are increased or provision of adequate calories is compromised, should be observed closely and promptly treated with a low threshold for hospital admission (see Table 7).

Prevention of Secondary Complications

One of the most important components of management (as it relates to prevention of secondary complications) is education of parents and caregivers such that diligent observation and management can be administered expediently in the setting of intercurrent illness or other catabolic stressors (see also Tables 5 and 6).

Table 8. Prevention of Secondary Manifestations in Individuals with Carnitine-Acylcarnitine Translocase (CACT) Deficiency

Manifestation/ Situation	Prevention	Considerations/Other
Acute encephalopathic crisis	• Intensive & ongoing education of affected persons & caregivers re natural history, maintenance & emergency treatment, prognosis, & risks of acute encephalopathic crises • Treatment protocols & provision of emergency letters or cards to incl guidance for care in the event of illness while on vacation • MediAlert bracelets/pendants, or car seat stickers • Adequate supplies of specialized dietary products (carbohydrate-only formulas or other caloric sources); maintain medication required for maintenance & emergency treatment (carnitine, antipyretics) at home.	• Provide written protocols for maintenance & emergency treatment to parents & primary care providers/pediatricians, teachers, & school staff. [1, 2] • Provide emergency letters/cards summarizing key information & principles of emergency treatment for CACT deficiency & incl contact info for primary treating metabolic center. • For any planned travel or vacations, consider contacting a center of expertise near the destination prior to travel.
Surgery or procedure (incl dental procedures)	• Notify designated metabolic center in advance of procedure to discuss perioperative mgmt w/surgeons & anesthesiologists. [3] • Emergency surgeries/procedures require planning input from physicians w/expertise in inherited metabolic diseases (w/respect to perioperative fluid & nutritional management).	Consider placing a "flag" in affected person's medical record so that all care providers are aware of the diagnosis & the need to solicit opinions & guidance from designated metabolic specialists in the setting of certain procedures.

1. Essential information including written treatment protocols should be in place in anticipation of possible future need for inpatient emergency treatment.
2. Parents or local hospitals should immediately inform the designated metabolic center if: (1) temperature rises >38.5°C (101°F); (2) vomiting/diarrhea or other symptoms of intercurrent illness develop; or (3) new neurologic symptoms appear.
3. Perioperative/perianesthetic management precautions may include visitations at specialist anesthetic clinics for affected individuals deemed to be at high risk for perioperative complications.

Surveillance

In addition to regular evaluations by a metabolic specialist and metabolic dietitian, the following are recommended.

Table 9. Recommended Surveillance for Individuals with Carnitine-Acylcarnitine Translocase (CACT) Deficiency

Manifestation	Evaluation	Frequency/Comment
Poor growth	Measure growth & head circumference.	At each visit
Delayed acquisition of developmental milestones	Monitor developmental milestones.	
	Neuropsychological testing using age-appropriate standardized assessment batteries	As clinically indicated
	Standardized quality-of-life assessment tools for patients & parents/caregivers	
Hypoglycemia	Serum glucose levels	Lab monitoring frequency should depend on patient's metabolic status. In general: • Neonates: every 2 wks • Infants age 2 mos – 1 yr: every 1-3 mos • Children ≥ 1 year: every 3-6 mos
Hyperammonemia	Serum ammonia levels	
HyperCKemia	Plasma total CK levels	
Abnormal liver function	ALT, AST, albumin	
Arrhythmias	EKG or 24-hr Holter test	Periodically as clinically indicated
Cardiomyopathy or cardiac dysfunction	Echocardiogram	Annually or as clinically indicated
Renal insufficiency	Plasma creatinine, BUN, electrolytes &/or cystatin C level	As clinically indicated
Nutritional monitoring for anemia, protein malnutrition, micronutrient or vitamin deficiencies	CBC, ferritin level, prealbumin, CRP [1], essential fatty acids, calcium, magnesium, phosphate, copper, zinc, selenium, folate, & vitamins A, D, E, & B_{12} levels	Annually after age 1 yr
New neurologic symptoms or somnolence	Consider EEG or neuroimaging (e.g., brain MRI).	As clinically indicated

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CK = creatine kinase; CRP = C-reactive protein

1. CRP is used as an inflammatory marker in the authors' practice, in conjunction with prealbumin. Prealbumin has a shorter half-life (2 to 3 days) than albumin and is thus a more favorable marker for acute nutritional changes. Prealbumin levels could be affected (decreased) by the presence of an acute inflammatory process; CRP is required to rule out that possibility [Keller 2019, Eckart et al 2020].

Agents/Circumstances to Avoid

Avoid the following:

- Prolonged fasting
- Catabolic illness (fever, intercurrent infection)
- Inadequate caloric provision during other stressors, especially when fasting is involved (surgery or procedure requiring fasting/anesthesia)
- Strenuous physical activity
- Anesthetics that contain high doses of long-chain fatty acids, such as propofol, although use for short procedures is likely to be tolerated [Urban et al 2019, Yu et al 2022]

Evaluation of Relatives at Risk

Testing of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment of CACT deficiency. For at-risk newborn sibs when prenatal testing was not performed: In parallel with newborn screening either test for the familial *SLC25A20* pathogenic variants or measure acylcarnitine profile.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Carnitine-acylcarnitine translocase (CACT) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *SLC25A20* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an *SLC25A20* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *SLC25A20* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *SLC25A20* pathogenic variants and therefore being unaffected.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with CACT deficiency are obligate heterozygotes (carriers) for a pathogenic variant in *SLC25A20*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC25A20* pathogenic variant.

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk relatives requires prior identification of the *SLC25A20* pathogenic variants in the family.

Biochemical testing. The efficacy of biochemical testing in detecting carriers has not been consistently explored; therefore, biochemical testing is not reliable at this time.

Related Genetic Counseling Issues

See **Management**, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *SLC25A20* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Biochemical testing. Fatty acid oxidation studies and/or CACT enzyme activity on cultured trophoblasts or amniotic cells has been used to confirm the molecular results of one individual in a cohort of nine pregnancies [Costa et al 2003].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  CACT Deficiency
- **MedlinePlus**
  Carnitine-acylcarnitine translocase deficiency
- **FOD Family Support Group (Fatty Oxidation Disorder)**
  Phone: 517-381-1940

Email: deb@fodsupport.org; fodgroup@gmail.com
fodsupport.org

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Carnitine-Acylcarnitine Translocase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC25A20	3p21.31	Mitochondrial carnitine/acylcarnitine carrier protein	SLC25A20 database	SLC25A20	SLC25A20

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Carnitine-Acylcarnitine Translocase Deficiency (View All in OMIM)

212138	CARNITINE-ACYLCARNITINE TRANSLOCASE DEFICIENCY; CACTD
613698	SOLUTE CARRIER FAMILY 25 (CARNITINE/ACYLCARNITINE TRANSLOCASE), MEMBER 20; SLC25A20

Molecular Pathogenesis

Fatty acid β-oxidation is an important pathway for energy production during times of stress or fasting, particularly in energy-demanding tissue such as cardiac muscle, skeletal muscle, and liver. Long-chain fatty acids require a carnitine shuttle system to be transported from the cytosol into the mitochondrial matrix for this purpose. Carnitine acylcarnitine translocase (CACT) transfers acylcarnitines formed by the action of carnitine palmitoyl-transferase I (CPT1) in the outer mitochondrial membrane into the mitochondrial matrix in exchange for free carnitine. These acylcarnitines are then converted into acyl-CoA by carnitine palmitoyl-transferase 2 (CPT2), to enter β-oxidation [Indiveri et al 2011].

In CACT deficiency, fatty acid β-oxidation is not able to proceed normally and, therefore, the energy sources for essential body functions are limited. The organs primarily affected subsequently utilize other energy sources, such as glycogen and protein. As these metabolites are depleted, hypoglycemia, hyperammonemia, and rhabdomyolysis (due to protein catabolism) supervene.

Mechanism of disease causation. Loss of function

***SLC25A20*-specific laboratory technical considerations.** A pseudogene (*CACTP*) has been mapped to chromosome 6p12. The intronless sequence of 558 nucleotides shows 88.6% homology to *SLC25A20* [Viggiano et al 1997].

Table 10. Notable *SLC25A20* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment
NM_000387.6 NP_000378.1	c.82G>T	p.Gly28Cys	Common pathogenic variant for mild neonatal-onset or later-onset form in persons of Pakistani or Indian descent [Morris et al 1998, Ryder et al 2021]
NM_000387.6	c.199-10T>G (c.261-10T>G or -10T>G intron 2)		Common pathogenic variant for neonatal-onset form for those of East Asian and Southeast Asian descent [Ogawa et al 2000, Hsu et al 2001, Lee et al 2011, Wang et al 2011, Vatanavicharn et al 2015, Tang et al 2019]
NM_000387.6 NP_000378.1	c.270delC	p.Phe91fs	Pathogenic variant for neonatal-onset form in persons of Turkish descent [Hsu et al 2001, Gürbüz et al 2021]
	c.713A>G	p.Gln238Arg	Pathogenic variant for neonatal-onset form in persons of Middle Eastern descent [Al Aqeel et al 2003, Galron et al 2004, Iacobazzi et al 2004b]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions.

Chapter Notes

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